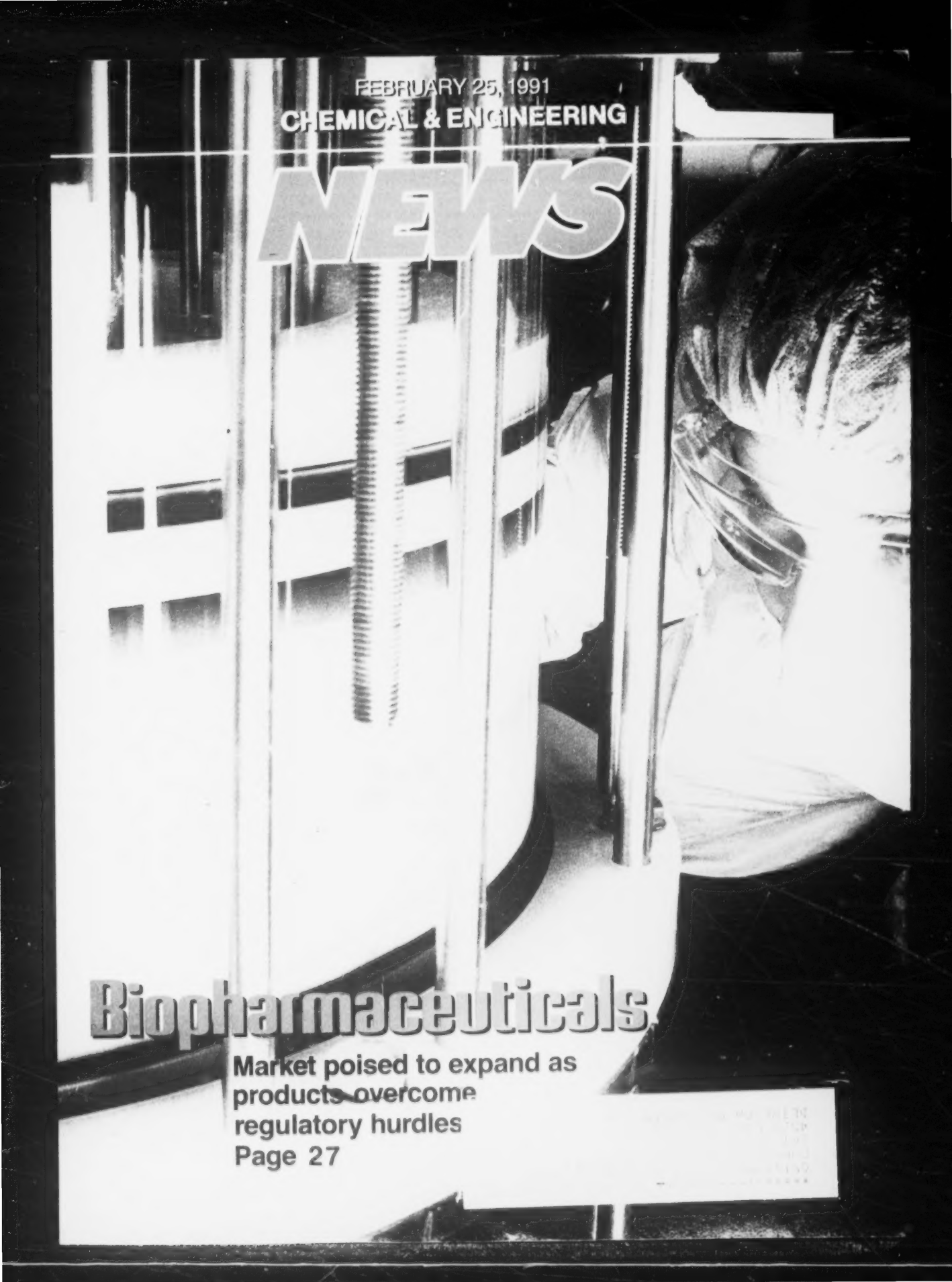
FEBRUARY 25, 1991
CHEMICAL & ENGINEERING

# NEWS



## Biopharmaceuticals

**Market poised to expand as products overcome regulatory hurdles**

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CHEMICAL & ENGINEERING
NEWS
FEBRUARY 25, 1991

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*Cover:* Amgen employee examines purification column used in production of erythropoietin

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# LETTERS

## Uranium health hazard

There is a letter to the editor (C&EN, Feb. 4, page 2) that may carry adverse consequences for our war against Iraq unless prompt, proactive action is taken. This letter, from Leonard A. Dietz of Schenectady, N.Y., makes a claim that the use of depleted uranium in shells from the M1-A1 tank and A-10 attack airplane will expose soldiers and civilians involved in the Iraq war to radioactive contamination. Dietz paints a particularly dire set of possible outcomes including high doses of radiation being delivered to lung tissue from very fine particles of uranium and uranium oxide that are produced when a depleted uranium shell strikes any object after being fired.

I believe that the radiation levels discussed in the Dietz letter indicate that the dangers from the shells are far less severe. Some simple calculations illustrate the point. He claims the radioactivity level is 150 microcuries per 387 g of depleted uranium. The radioactivity would then be $3.87 \times 10^{-1}$ microcuries per g or $3.87 \times 10^{-1}$ picocuries per $\mu$g. Since the density of uranium is approximately 18.95, a cube of uranium 1 $\mu$m on a side (volume = $10^{-12}$ cc, a micrometer-size particle) would have a mass of $1.895 \times 10^{-11}$ g. Therefore, the radioactivity of a single particle would be $7.33 \times 10^{-12}$ microcuries. Since a microcurie is $3.67 \times 10^{+4}$ disintegrations per second, a given particle would have a disintegration rate of about $2.69 \times 10^{-7}$ disintegrations per second, or about once every 0.85 year. This is a rather low level of radioactivity.

I have considerable expertise in the area of biological effects of high atomic weight radionuclides, since my Ph.D. thesis was in this area.

**Gene A. Nelson**
*President, Biophysics Co.*
*Cleveland, Ohio*

## Quantized transition state

An account by Rudy Baum about theoretical predictions of quantized transition-state structure in the $H + H_2$ reaction (C&EN, Jan. 28, page 21) failed to mention very similar, earlier work on the $O(^3P) + H_2$ reaction [Bowman, J. M., *Chem. Phys. Lett.*, **141**, 545 (1987)]. In that paper, transition-state structure in the cumulative reaction probability was reported.

Actually, two cumulative reaction probabilities were examined: one was from exact quantum calculations [Haug, K., Schwenke, D. W., Truhlar, D. G., Zhang, Y., Zhang, J. Z. H., Kouri, D. J., *J. Chem. Phys.*, **87**, 1982 (1987)]; and the other was from approximate quantum calculations (based on a reduced dimensionality adiabatic bend theory) that I had done. The exact and approximate cumulative reaction probabilities were in very good agreement with each other, and both showed structure analogous to that reported for $H + H_2$ by Chatfield et al. [Chatfield, D. C., Friedman, R. S., Truhlar, D. G., Garrett, B. C., Schwenke, D. W., *J. Am. Chem. Soc.*, **113**, 486 (1991)] and reported in the Baum article.

**Joel M. Bowman**
*Department of Chemistry*
*Emory University*

## Safety precautions

The chemical safety letter on a carbodiimide eye irritant (C&EN, Nov. 5, 1990, page 2) is a classic case of poor safety when dealing with chemical spills. Most responsible environmental firms insist their employees use full face respirators. Why? Ronald C. Moyer of Tuxedo, N.Y., has proven the value of eye protection from vapors as well as from physical dangers. Being donned with improper safety equipment can be as serious a blunder as taking no safety precautions at all.

**James S. Smith**
*President/Chemist*
*Trillium Environmental Consultants*
*Coatesville, Pa.*

## Recruiting for science

The spectacles of the various bowl parades on television on New Year's Day raised a major question in my mind. How is it that so many schools are able to rouse so much enthusiasm for the marching bands that were a major feature in these parades? There were thousands of young people showing such a dedication to their craft that it was obvious that some force or forces were operating here that might be harnessed in other ways. One other way that will be obvious to many of your readers is in the recruitment and training of our young people in the sciences and mathematics.

It is pretty obvious that the teachers and coaches of bands and of parade discipline must be highly dedicated. Otherwise, how would they be able to arouse such interest in activities that require

# Sales, Earnings of Canadian Chemical Companies Suffer in 1990

**Financial results could have been worse, however, as most major firms weathered the recessions at home and in the U.S. better than expected**

With both their domestic economy and their major export market (the U.S.) in recession, Canadian chemical companies limped out of 1990 in fairly good shape.

True, sales of most major Canadian chemical companies were down in 1990, particularly in the fourth quarter. Profits were down even more. But it could have been worse. Gerald P. Elden, president of Celanese Canada, called his firm's results "quite good and particularly gratifying," considering the state of the Canadian economy and the negative business environment. And Gordon R. Wittman, president and chief operating officer of Du Pont Canada, said that, despite the poor economic climate, several of his firm's products came through with higher earnings.

Those higher earnings were chalked up by such products as adipic acid, medicinals, and specialty polymers. But, they were not enough to offset lower earnings in Du Pont Canada's other product lines. As a result, Du Pont Canada's net income last year slid a hefty 28% from 1989 to $54 million, even though sales declined a minuscule 0.7% to $1.22 billion. It could have been worse had it not been for exports.

Under the Free Trade Agreement (FTA) between Canada and the U.S., tariffs on many chemical products were completely eliminated. This allowed Du Pont Canada to increase significantly its exports of several products to the U.S. In fact, the company's exports in 1990 rose 38% from the previous year to $347 million, with most of those exports moving into the U.S.

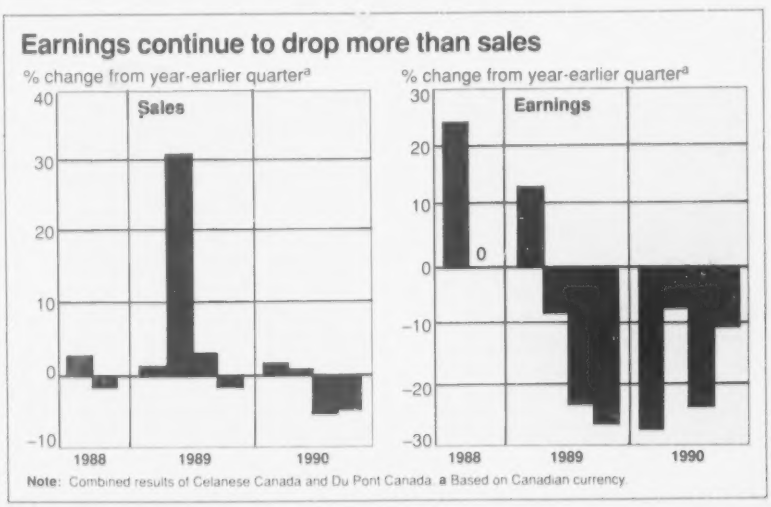
Du Pont Canada's export performance was better than that of most Canadian chemical companies. Through the first 10 months of the year (latest data available), Canadian chemical exports were up only 5%.

Du Pont Canada was one of the few fortunate Canadian chemical companies to enjoy a profitable fourth quarter. Although sales were down 4.6% from the year-earlier quarter to $282 million, net income advanced a healthy 23% to $8.9 million. One possible reason: higher prices on some commodity petrochemicals and plastics.

Celanese Canada, however, wasn't as fortunate in the fourth quarter. Sales were down 7.7%, but profits slid 34%. For the full year, Celanese Canada racked up sales of $316 million, down 8% from 1989. Profits, however, dropped almost 15% to $35.8 million. One reason for the company's poor fourth-quarter performance was its textile group's polyester unit. It was hit by a combination of weak markets, lower selling prices, and higher raw material costs. Weak markets for cellulosics also hurt the company's bottom line. And methanol prices were generally lower in 1990 than they were in 1989, although they did improve toward the end of the year.

Union Carbide Canada's financial results for 1990 are confusing because the company has been—and still is—undergoing a series of reorganization moves. Under the most recent proposal, parent company Union Carbide is bidding to buy the minority shares of Union Carbide Canada. It already owns 75% of the Canadian company.

This proposal supercedes an earlier plan under which Carbide Canada would have sold its chemicals and plastics business to its parent. As a result, Carbide Canada's chemicals and plastics operations were classified as "discontinued operations" at the end of last year's third quarter. For the first nine months of



## Canadian chemical companies hit rough times

| $ Millions[a] | Net sales | % change from 1989[b] | Net income[c] | % change from 1989[b] | Profit margin[d] 1989 | Profit margin[d] 1989 |
|---|---|---|---|---|---|---|
| **FOURTH-QUARTER 1990** | | | | | | |
| Celanese Canada | $ 79.9 | -7.7% | $ 6.8 | -33.6% | 8.6% | 11.9% |
| Du Pont Canada | 281.6 | -4.6 | 8.9 | 22.6 | 3.2 | 8.5 |
| Nova Corp.[e] | 628.5 | -13.4 | 87.6 | 140.5 | na | na |
| Union Carbide Canada[f] | 48.1 | -3.9 | -2.7 | na | na | 6.1 |
| **FULL-YEAR 1990** | | | | | | |
| Celanese Canada | $ 316.1 | -8.1% | $ 35.8 | -14.5% | 11.3% | 12.2% |
| Du Pont Canada | 1222.3 | -0.7 | 54.1 | -27.9 | 4.4 | 6.1 |
| Nova Corp.[e] | 2857.3 | -2.1 | 323.4 | -31.1 | na | na |
| Union Carbide Canada[f] | 216.8 | 6.7 | 7.2 | -53.9 | 3.3 | 7.7 |

a Based on recent exchange rate of $1.00 = $1.54 (Canadian). b Based on Canadian currency. c Based on continuous operations and excluding extraordinary items. d Net income as percentage of sales. e Includes petrochemical, plastics, and rubber operations only. Nova does not break out net income by division. Income shown is operating income, which does not compare with net income of other companies. f Pending company reorganization, data include continuing operations of Linde Division only; they do not include chemicals and plastics. na = not applicable.

1990, chemicals and plastics lost $1.25 million.

Now only industrial, medical, and specialty gases remain as Carbide Canada's "continuing operations." Although sales of these products rose 6.7% last year to $217 million, profits plummeted 54% to $7.2 million.

Whether Canadian chemical companies can move into the black this year depends, of course, on the economy in Canada and the U.S. Celanese Canada's Elden says the 1991 outlook is "unpredictable." But Du Pont Canada's Wittman expects difficult economic conditions to continue well into 1991.

*Earl Anderson*

# Hazardous waste management industry to grow

Demand for hazardous waste management, heavily impacted by environmental concerns and state, local, and federal policies, is expected to more than double by 1995. According to a forecast by Leading Edge Reports, a Cleveland-based market research firm, the $73 billion hazardous waste treatment and disposal market will grow to about $174 billion by 1995. The service sector will continue to account for about 7 to 8% of this market.

Since 1984, the demand for services such as environmental testing, consulting, analysis, transportation, and remediation has grown 21% annually to more than $6 billion in 1990. Transportation makes up more than 50% of this market, followed by consulting and engineering at 20% and remediation at 15%. Whereas 96% of hazardous waste now is treated on site by a few larger companies, as regulations broaden and become more stringent, the need for services will grow among small and medium-size companies without such capabilities. By 1995, service revenues are projected to reach $12.1 billion.

The mature land disposal market, which accounts for 75% of hazardous waste managed, is expected to grow only 2.3% annually because of stricter Environmental Protection Agency regulations. But its value will increase more than 7% annually to about $54 billion in 1995, as disposal costs rise. The amounts of hazardous waste managed through incineration, treatment (physical, chemical, or biological), and recycling are expected to more than double by 1995.

*Ann Thayer*

### Chemical industry leads in hazardous waste output

| Billions of lb | 1990 | 1995 |
|---|---|---|
| Chemicals & allied products | 373 | 470 |
| Primary metals | 119 | 143 |
| Petroleum & coal | 88 | 110 |
| Fabricated metal | 68 | 86 |
| Rubber & plastic | 42 | 60 |
| Other | 71 | 90 |
| TOTAL | 761 | 959 |

Source: Leading Edge Reports

# Spectrum Chemical opens East Coast plant

Spectrum Chemical opened its new facility in New Brunswick, N.J., earlier this month to provide fine chemicals to customers in the East. The new facility thus joins Spectrum's established unit at Gardena, Calif.

Spectrum is a privately held manufacturer and distributor of research chemicals and reagents. Since the middle of 1990, the company also has been the exclusive North American distributor for Janssen Chimica, which produces more than 12,000 organic chemicals at its plant in Belgium. Janssen Chimica is the chemicals division of Janssen Pharmaceutica, a wholly owned subsidiary of Johnson & Johnson.

Paul Berg, president of Spectrum says that the new unit, besides producing Spectrum products, warehouses more than 10,000 Janssen chemicals. Presently, it also holds about 2000 Spectrum products, which ultimately will be increased to 4000.

The East Coast facility is essentially the reverse of that in the West, which focuses more on Spectrum products and is lighter on the chemicals coming from Janssen.

Paul DiMarco, plant manager of the new facility, says that the site was chosen primarily because of the large number of pharmaceutical companies in the New Jersey area. These companies, using Spectrum's products in research, provide a good potential customer base.

In broadening its line and scope, Spectrum is going up against a number of fine chemicals suppliers, including J. T. Baker, Alfa, Mallinckrodt, Eastman Kodak, and, of course, Sigma-Aldrich, which is perhaps the largest in the breadth of its product line.

*William Storck*

# Hybrid systems improve membrane technology

The idea of using membrane separation as a way of conserving energy is gaining more attention. To get a better insight into the strengths and weaknesses of this approach, for example, the Department of Energy has sponsored several projects aimed at promoting separations with membranes. One of these projects, just completed, was aimed at determining the broad rules for applicability of membrane separators in some of the larger industrial processes.

Membranes offer an attractive means for component separation in process streams, their appeal centering on the energy conservation possible. But they also have intrinsic limitations that restrain their usefulness as stand-alone units. Hence, economic pressures are prompting the use of membrane separators in concert with conventional separation technology. These hybrid units optimize performance at least cost.

Guidelines for designing and specifying hybrid units are only now being developed. More extensive use of membrane separators will require demonstration of their effectiveness in a broader spectrum of applications, technical education, and development of some new membrane materials.

The greatest appeal of membranes has always been their low energy consumption. The most successful high-volume applications to date have been in separation of high-volume gas stream components and desalination of seawater by reverse osmosis. There have also been numerous applications of membrane separations in clinical analysis and in specialized membrane reactors for high-value products. However, membrane separators are potentially usable in a much wider variety of industrial processing, suggesting greater application than they have experienced.

The new DOE project was carried out by Douglas E. Gottschlich and Daryl Roberts of SRI International. The final report on the project has just been issued by DOE.

The report recognizes that although membrane technology has provided a new means for materials separation, it has economic limitations. The present consensus is that membrane operations are best conducted, and are more economical, when carried out in conjunction with conventional technology. The SRI report lists the criteria for selecting a hybrid membrane system. The focus is on energy consumption of the hybrid, compared to that of membranes alone or conventional technology alone.

**Largest energy users have room for savings**

| Industry | Energy purchased, trillion Btu |
|---|---|
| Chemicals | 2630 |
| Primary metals | 2241 |
| Pulp and paper | 1262 |
| Oil refining | 1137 |
| Stone/clay/glass | 1078 |
| Food | 913 |
| TOTAL | 9261 |

Source: Department of Commerce (most recent available data)

The general methodology used in the SRI study was to consider numerous industrial separations and identify those that appeared to be amenable to membrane separations. Four particular examples were then selected for detailed evaluation. These were propane/propylene separation, removal of nitrogen from natural gas, concentration of kraft black pulp liquor, and solvent deasphalting.

All of these processes appear to be on the verge of commercial viability, and they provided the means to extract the general criteria that would apply to any hybrid system for industrial use. The criteria were then used to identify 10 separations that the investigators consider worthy of further development by DOE. The principal guides to selecting promising hybrid systems were thermodynamic and economic.

The most recent available data from the Commerce Department put total U.S. industrial energy consumption at about 11,500 trillion Btu, with roughly 80% being consumed by six industries. All employ extensive separation processes; the major conventional ones are distillation, absorption/stripping, adsorption, ion exchange, extraction, precipitation and crystallization, and filtration. The most energy-intensive of these processes involves a single phase from which two phases of different compositions must be generated. The two phases are then separated by gravity or filtration. The energy (usually heat) required to generate the phases is quite large.

The investigators noted that membranes don't usually produce high-purity products. But neither do they require phase changes, and they are particularly useful in bulk separations. Combining the membrane with more conventional technology should, in principle, provide a hybrid with optimum characteristics.

Those hybrids that demonstrated significant energy savings in a novel application, for which adequate process data were available, and which exhibited a likelihood of being commercially acceptable were considered prime candidates for the "Best-10" list in the report. In all cases the candidate process was simulated with a commercial computer program, evaluated thermodynamically on the basis of the change of availability in the process stream, the availability of the utility streams, the extent of separation, and thermodynamic efficiency. The economic process cost was defined as the cost necessary to transform feed into product.

Given that a hybrid system is technically feasible, the most important criterion for selecting a hybrid system appears to be energy con-

**Ten systems are prime energy-saving candidates**

| System | Potential energy saving, trillion Btu per year |
|---|---|
| Propane/propylene separation | 13 |
| Natural gas dehydration | 10–12 |
| Deasphalting of oil | 10 |
| Ethane/ethylene separation | 6 |
| Sour-water stripping | 6 |
| Inorganic acid dehydration | 5 |
| Acetic acid dehydration | 3 |
| Ammonia manufacture | 2 |
| Methyl *tert*-butyl ether manufacture | 1–2 |
| Urea manufacture | 1–2 |

sumption. The selection rule in this regard is that a membrane hybrid is unlikely to be used unless it would require at least one third less energy than a nonmembrane technology. The 10 processes recommended for further investigation reflect the importance of this criterion.

The emphasis on energy consumption in selecting hybrid systems may not be a universal criterion. Much also depends on the price of energy. Where energy is particularly expensive, there is growing evidence that stand-alone membrane systems can be successfully used over conventional separators. Such is suggested by Jimmy L. Humphrey, head of an engineering firm in Austin, Tex., specializing in separations.

Humphrey has recently returned from a trip to Japan and Europe and notes that in Europe there are at least 36 pervaporation systems now in production for dewatering alcohol mixtures. Mitsui in Japan has a new 500 kg-per-hour unit for dewatering isopropyl alcohol and at present is working on an acetone unit. Other membrane units are being used. The interest in stand-alone units, says Humphrey, is strictly economic, but the economics involve more expensive energy than that in the U.S., where energy is still relatively cheap. If cost of energy continues to increase, however, the selection criteria may change.

It remains unclear why membrane separations, either stand-alone or hybrid systems, are not more widely understood. One observer suggests that engineering education hasn't caught up with all the new unit processes and operations. If true, the problem should be corrected with time. Another believes that the tendency to "black box" training in separations technology obscures the basic character of the operations. Thus, separations can be considered as black box operations in which there are inputs, outputs, and parameters. Specifying a separation technique for a process amounts to nothing more than keying the appropriate parameters into a simulation program. This approach, while very appealing to computer buffs, doesn't provide much insight into the physical realities of the process.

*Joseph Haggin*

## SOFTWARE/DATABASE UPDATE

*Software/Database Update provides readers with information about new chemistry-related computer programs. Vendors may submit relevant press releases to Software/Database Update,* Chemical & Engineering News, *1155—16th St., N.W., Washington, D.C. 20036.*

■ **Polaris** and **Enzymix** (Molecular Simultations, $35,000 to $55,000 for both programs, Circle 301) are new modules for the BIOGRAF molecular modeling program. Polaris models electrostatic and solvation free energies of proteins and other species. Enzymix models enzymatic reactions, including bond-making and -breaking, reaction trajectories, and electrostatic energies of charged groups. The programs run on Stardent and Silicon Graphics workstations. The original versions were written by chemistry professor Arieh Warshel of the University of Southern California.

■ **Structural Ceramics Database** (National Institute of Standards & Technology, $495, Circle 302) provides information on thermal and mechanical properties of silicon carbide and silicon nitride monolithic materials, used in heat exchangers, engine components, sensors, and cutting tools. It runs on IBM PCs and PS/2s.

■ **Dortmund Data Bank** (Technical Database Services, price depends on number of modules ordered, Circle 303), a database of phase equilibrium and physical property data for pure components and mixtures, is now available in a version for IBM PCs and compatibles. Databases on vapor-liquid equilibrium, liquid-liquid equilibrium, heats of mixing, activity coefficients, gas solubility, and excess heat capacity can be ordered singly or in combination.

■ **Chem-X** (Chemical Design, $8000 and up, Circle 304), a molecular modeling program, is now available for IBM RS/6000 workstations, in addition to the Silicon Graphics, VAXStation, Apple Mac II, and IBM PC versions currently offered. The RS/6000 accommodates 3-D database building and quantum mechanics calculations, with adequate graphics for small molecules.

■ **SMILES** (Daylight Chemical Information Systems, $4000 and up [single user], Circle 305), a chemical nomenclature program, is now available as a programer's toolkit for the UNIX and VMS operating systems. The program is callable from C, Fortran, Pascal, and Lisp.

■ **Chem3D** and **Chem3D Plus** (Cambridge Scientific Computing, $595 and $895, respectively; Circle 306), molecular modeling software for the Apple Macintosh, are available in version 3.0, which includes new 3-D rotation tools and other enhancements. Chem3D Plus has energy minimization and molecular dynamics capabilities in addition to all of Chem3D's model building and manipulation functions.

■ **DigiMatic** (FEB Software, $229, Circle 307), a digitizer program for the Apple Macintosh, converts charts, graphs, or plots from existing sources (like technical journals) into editable numeric data.

■ **GRA-FIT** (JR Systems, $195, Circle 308) is a 2-D plotting system for IBM PCs. Options for displaying data include 14 plot symbols, five linear regression models, and Fourier transform-based smoothing.

■ **CERCLIS** (Chemical Information Systems, Circle 309), an online database of hazardous waste sites and incidents, now includes EPA's list of parties potentially responsible for cleanup costs at Superfund sites.

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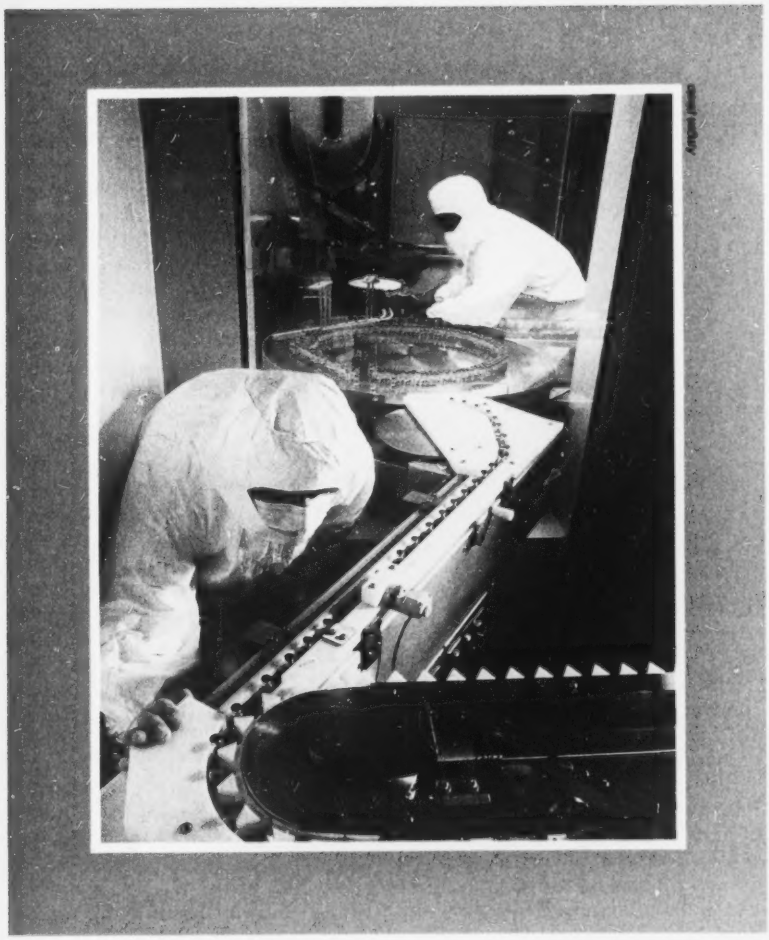


# Biopharmaceuticals Overcoming Market Hurdles

**Ann M. Thayer,**
C&EN Northeast News Bureau

Licensing, patent protection, and getting through the regulatory process have become as much a concern to fledgling biotechnology companies as developing new products.

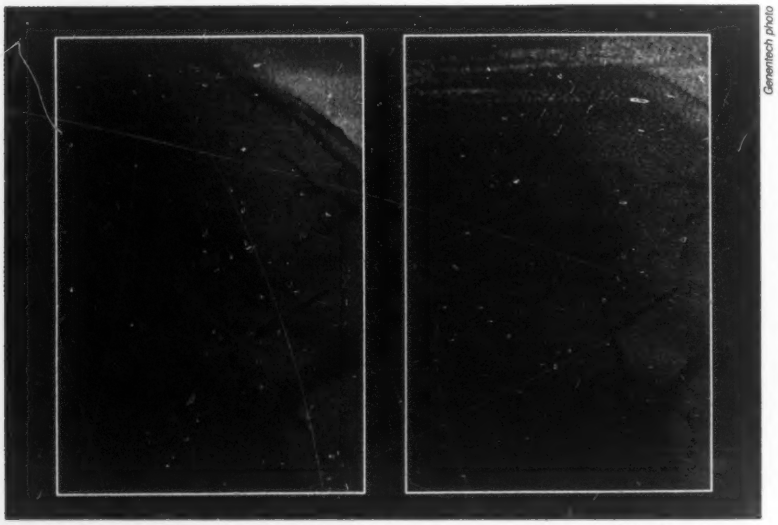
Of the products developed by biotechnology, human therapeutics have been the most important, says Roger E. Shamel, president of Consulting Resources Corp., accounting for nearly two thirds of biotechnology product sales. The Lexington, Mass.-based market consulting firm estimates that U.S. sales of biopharmaceuticals will be about $1.2 billion in 1991—a somewhat surprising statistic in light of only 12 products having made it to market.

Twelve product approvals in nearly as many years is testament to how slow movement has been. Through the 1990s, a steady stream of products is expected as companies make it past development and regulatory hurdles, expanding the market to nearly $8 billion by the end of the decade. This is because there are more than 20 applications for approval filed with the Food & Drug Administration and nearly as many drugs in the final stage of clinical studies. Although position on the regulatory ladder is no guarantee of near-term marketability, the most likely new products anticipated are a wide range of therapeutic agents with broad biological activities—colony-stimulating factors, interferons, interleukins, growth and blood factors, and monoclonal antibodies. In addition, expanded uses and second-generation versions of already approved drugs will contribute to industry growth.

Although the majority of new biopharmaceuticals now are sold by major pharmaceutical firms, experiences in bringing the first products to market have broken ground, identifying stumbling blocks for biotechnology companies that will be marketing the newer products. "There are a number of easily identified impediments to getting new biotechnology products to the market," says Richard D. Godown, president of the Industrial Biotechnology Association (IBA), "which, if corrected, would smooth the path." In addition to regulatory processes, these include issues of intellectual property protection, orphan drug law, drug pricing, and health care reimbursement.

Early beliefs that products, being based on "natural" human proteins, would be reviewed rapidly and favorably by FDA have been replaced by a degree of uncertainty, say observers. Although a few biopharmaceuticals have moved through the regulatory process as fast or faster than some traditional therapeutics, some industry executives still express frustration with FDA and the time required for product approval. The U.S. agency generally is viewed as the most cautious of worldwide regulatory groups.

A broad review of FDA is being conducted by an advisory committee to the U.S. Department of Health & Human Services, chaired by Charles C. Edwards, president and chief executive officer of Scripps Clinic & Research Foundation. In an interim report published in September 1990,



Genentech photo

*Angiograms showing blood flow in blocked coronary arteries (left) indicate improvement after treatment (right) with TPA*

the Edwards committee described FDA as an "agency under stress," faced with conflicting demands, limited resources, and the need for enhanced leadership and strengthened management systems. And, although finding no immediate risk to public health and safety, it believes FDA's ability to operate is being challenged by the growing number and complexity of products coming before it, coupled with increased responsibilities and lagging resources. A final committee report is due out in May 1991.

In November, Godown appeared before the committee and proposed several steps aimed at streamlining the drug approval process. At the top of his list was improving the stature and powers of the FDA Commissioner within HHS. Other suggestions were designed, Godown says, to improve resource allocation, to update existing rules and regulations, and ultimately to expedite approval of safe biotechnology products.

These suggested changes also include the deregulation of certain noncommercial clinical research and increased guidance by FDA as it becomes more familiar with biotechnology. IBA stressed that FDA should "examine all of its regulatory programs to insure that biotechnology product development is not hindered." One possible route is the approval of drugs for life-threatening conditions after Phase II efficacy trials, followed by postmarketing surveillance programs.

IBA also supports the expanded role of advisory committees in the product development and regulatory cycle. These are outside groups brought in when needed to evaluate and make nonbinding recommendations for or against approval. "It's clear that the position of advisory committees should be enhanced," says Godown, "so that when this group of outside, preeminent experts in an area suggest that something is satisfactory, they should have the burden of proof." FDA's Biological Response Modifiers Advisory Committee met for the first time last year. With several companies going before it with products, industry executives are expressing the belief that such appearances may become a regular part of the approval process.

The first biopharmaceuticals approved were human insulin and human growth hormone, genetically engineered versions of existing products isolated from animal sources. As such, says one industry executive, the transition to market was relatively easy since conceptually they were "easy sells," unlike later products to appear before FDA. Many drugs based on recombinant proteins or monoclonal antibodies are presenting FDA not only with a new technology, but often with what are unfamiliar treatment modalities to thus far unsuccessfully treated diseases.

FDA since has approved another human growth hormone, a therapeutic monoclonal antibody, two $\alpha$-interferons, two hepatitis B vaccines, a tissue plasminogen activator, and a haemophilus B vaccine. In the past two years, erythropoietin (EPO) and $\gamma$-interferon were approved. Positive advisory committee recommendations have been made for two colony-stimulating factors. Biotechnology companies behind the products include Amgen, Biogen, Chiron, Genentech, and Praxis Biologics, now owned by American Cyanamid. Genentech alone accounts for five products, three of which it markets itself.

After licensing its $\alpha$-interferon to Hoffmann-La Roche and insulin to Eli Lilly, Genentech went on to become the first biotechnology company to manufacture and market its own drug product. Human growth hormone (HGH), used to treat children with pituitary growth hormone deficiencies, has had double-digit annual growth and reached $155 million in sales in 1990, or about 75% of the market, says Jerry Beers, director of marketing for Genentech. The remaining market goes to Lilly's version of HGH.

Both companies have orphan drug status for HGH. The Orphan Drug Act was designed to offer incentives to companies to develop drugs for rare diseases, markets generally assumed to offer limited opportunities to recoup the high costs of drug development. The most important incentive is a seven-year market exclusivity to the first company to win approval for a drug designated as an orphan drug for a particular disease indication. Orphan drug status may be obtained for similar, but structurally different, drugs. However, clear definitions of what is meant by different have not been determined by FDA, and instead are being defined on a case-by-case basis.

One amino acid difference was enough for FDA to consider the Genentech and Lilly products as different and award orphan status to both. At least two other companies have applications pending with FDA for approval of HGH but are effectively blocked unless able to convince FDA

## FDA process for approving new drugs takes many steps

Although only 12 biotechnology drugs have been approved, data compiled by the Pharmaceutical Manufacturers Association show that more than 100 genetically engineered drugs or vaccines were in clinical trials or under review by FDA at the beginning of 1990.

By the time final approval is sought, a drug product must have undergone several lengthy stages of testing and review. These stages consist of three phases of human clinical trials. First, an investigational new drug application, based on results from preclinical laboratory and animal tests for biological activity and safety, and information on drug manufacture, is filed. It becomes effective in 30 days unless denied by FDA.

Phase I of clinical trials consists of profiling the safety and pharmacological activity of a drug. Using a small number (less than 100) of healthy volunteers, not patients, Phase I trials are estimated to take less than one year to complete. Safe dosage amounts are determined as well as the duration of its action and how the drug is absorbed, distributed, metabolized, and excreted.

Phase II studies are the first step in efficacy tests on patients. Controlled studies on a population of about 200 to 300 volunteer patients are conducted along with coincident animal and human studies for safety. Such trials are expected to require about two years to complete.

With as much as 10 times the test population as in Phase II trials, Phase III trials are generally the most extensive of clinical studies, taking about three years to complete. The aim is to confirm prior efficacy results in patients afflicted with the specific disease. In addition, low-incidence adverse effects must be identified.

Upon completion of clinical trials, a product license application, as it is called by FDA's Center for Biologics Evaluation & Review, which handles biotechnology drug products, is filed. Containing all the data collected in preclinical and clinical studies, along with information on chemical structure, scientific rationale and purpose, and formulation and production details, such applications can be thousands of pages long. The FDA review and approval process takes an average of about two and a half years to complete.

Not including at least a couple years for preclinical studies, the entire clinical testing and approval process averages between seven and 10 years. FDA began a program for expedited drug approval in 1989. Its aim is to decrease the approval time for drugs for serious or life-threatening diseases. Based on promising results from Phase I, Phase II and Phase III studies may be combined for a savings of about two to three years.

Another program, which was started in 1987 in an effort to make promising investigational new drugs available to seriously ill patients early in the drug development process and before marketing approval is granted, is called treatment IND. To qualify for a treatment IND, no comparable or satisfactory therapy or drug can be available, the drug must have already completed or currently be in controlled clinical trials under an IND, and the sponsor of the trials must be seeking marketing approval. The overall review process, however, is not affected.

A company may also apply for an orphan drug designation from FDA under the 1983 Orphan Drug Act. The act was passed to encourage the development of drug products for rare diseases, defined as those affecting 200,000 or fewer individuals in the U.S. Although the drug approval process is unchanged, it provides tax incentives and seven years of marketing exclusivity to the first company receiving FDA approval for a designated orphan drug. Since the act was implemented, about 45 orphan drugs have been approved and more than 130 are in clinical testing or pending review.

that their products, too, are different. A recently proposed FDA regulation tightening the rules would bar approval of a similiar drug unless shown to be clinically superior to one already approved (C&EN, Feb 4, page 17). A product the same or similar to an orphan drug can still be approved for other uses.

Some exceptional biopharmaceuticals, namely HGH and EPO, have attracted attention by becoming very profitable orphan drug products. Many others approved or under development have been designated as orphan drugs. Amendments to the law, proposed in early 1990, divided the biotechnology community. Although passed by Congress, the amendments were vetoed by President Bush. The debate is expected to continue.

Early proposed changes sought to expand market exclusivity to those simultaneously developing products and to lower ceilings on the number of patients or on the amount of sales allowed for orphan drugs. The debate in part centers on whether companies with highly profitable products should have market exclusivity. On one side are those who believe that monopolies drive up prices and reduce availability, and that incentives already exist in what would be competitive markets. On the other side are those who say it is not possible to predict, when seeking orphan status in the early stages of investment and development, how lucrative a product will be.

The Pharmaceutical Manufacturers Association opposed changes viewed as weakening the orphan drug law, calling it "one of the most powerful incentives" in drug development and a significant factor in business decisions. Others are looking to expand the present incentives for what will probably be a majority of unprofitable orphan drugs.

"The problem with keeping the pot boiling on this issue is that it introduces uncertainty into the future of those products affected," says Godown. "This reflects on the small biotechnology companies working on orphan products, since if investors have the idea that the rules may change somewhere along the line, it becomes more difficult to attract investment." IBA opposed early amendments, which were retroactive, but supported the later modified amendments that Congress passed. Godown calls these an "honest compromise" that would have preserved existing orphan drug designations and market exclusivities.

Meanwhile, the HGH market is expected to continue to expand, says Beers, in its current treatment indication and in new areas. These include areas in which the company is conducting Phase II and Phase III trials and areas as diverse as Turner's syndrome, pediatric burns, and growth retardation related to renal insufficiency. A recent *New England Journal of Medicine* report on the effect of HGH in older adults has generated interest, but since actual long-term benefits and potential hazards are unclear, it is suggested cautiously that HGH may find some use in aiding recovery from illness or surgery.

"Growth hormone has been very successful from the standpoint of starting and running a company and providing revenues for additional R&D," comments Beers. What followed was approval in late 1987 for tissue plasminogen activator (TPA), a thrombolytic agent that dissolves blood clots and is used in treating heart attack patients. In 1990, U.S. sales of TPA by Genentech reached about $210 million, owing in part to growth of the market for thrombolytic agents. "Sales currently will probably remain somewhat level or grow slightly," says Beers. Boehringer Ingelheim, the company's licensee outside North America and Japan, has launched TPA in at least 20 countries and is now copromoting in the U.S.

***Epidermal growth factor is modeled on computer at Chiron's labs***

Although having about two-thirds market share, TPA has found new competition from lower priced streptokinase and Eminase, a streptokinase derivative sold by SmithKline Beecham. In March 1990, the results of a study, known as the GISSI-II trials, indicated no statistically significant difference in the performance of streptokinase and TPA. However, adds Beers, TPA was found to have fewer side effects.

The company stresses that the treatment protocol used in the study is not that favored in the U.S. Here, explains Beers, an anticoagulant and an antiplatelet aggregator are given simultaneously with TPA. There is also an ongoing debate as to whether TPA's reported ability to open more arteries faster than other agents translates into fewer deaths. At least two other trials comparing various thrombolytic agents are under way, but results are not expected for a few years.

Genentech is working actively to expand uses for TPA. An application was recently submitted to FDA for peripheral arterial occlusion, says Beers. Other possible uses being investigated in later-stage trials, if not already before FDA, are in the treatment of unstable angina, pulmonary embolism, and stroke.

The newest product for Genentech is γ-interferon. It was approved for treating chronic granulomatous disease, a rare genetic defect of the immune system that results in severe or life-threatening infections. Approved in late 1990 as an orphan drug, the company hopes to launch it in the next couple months.

"Like α-interferon, γ-interferon seems to have somewhat diverse biological actions," says Beers, "so the challenge is to follow leads with regard to biological activity and prove in the clinic that there is some value." Genentech soon will start Phase III trials for severe atopic dermatitis, he adds, and Phase III trials have been started for trauma-related infections. Although not proving to be a "magic bullet" for cancer, clinical trials are being pursued in some tumor types where activity has been seen.

Other areas of development include CD4 and DNase. The human immunodeficiency virus (HIV) is believed to bind with its gp120 surface protein to the CD4 protein on immune system T cells. Genentech is testing CD4 in combination with IgG, a human antibody fragment that may enhance the activity of the receptor, in Phase I trials. Definitive efficacy markers have not been seen, comments Beers, but are not necessarily to be expected in early trials not designed to demonstrate efficacy. In early trials, the company is also investigating a recombinant form of gp120 as a potential immune system booster in HIV infected, but otherwise healthy, patients.

DNase, a recombinant enzyme, is about to enter Phase II trials, says Beers. The company plans to file for orphan drug status for DNase in treatment of cystic fibrosis. Mucus secretions in cystic fibrosis patients consist of extracellular DNA released by inflammatory cells that ac-

## Erythropoietin leads U.S. biotech drug market

| $ Millions | 1991 | 1996 | 2001 |
|---|---|---|---|
| Cardiovascular | $ 600 | $1145 | $2250 |
| Erythropoietin | 350[a] | 800 | 1300 |
| Tissue plasminogen activator | 225[a] | 225 | 450 |
| Blood factors | 25[a,b] | 50 | 100 |
| Superoxide dimutase | 0 | 20 | 100 |
| Others | 0 | 50 | 300 |
| Cancer | 145 | 685 | 1850 |
| Colony-stimulating factors | 20[a,b] | 250 | 650 |
| Interferons | 125[a] | 200 | 350 |
| Interleukins | 0 | 210 | 550 |
| Others | 0 | 25 | 300 |
| Hormones/growth factors | 420 | 890 | 1605 |
| Epidermal growth factor | 0 | 65 | 230 |
| Human growth hormone | 250[a] | 470 | 650 |
| Human insulin | 170[a] | 250 | 325 |
| Others | 0 | 105 | 400 |
| Vaccines | 15 | 170 | 825 |
| AIDS | 0 | 50 | 300 |
| Herpes | 0 | 15 | 150 |
| Hepatitis B, others | 15[a] | 105 | 375 |
| Monoclonal antibodies | | | |
| Therapeutics | 20 | 200 | 490 |
| Others | 0 | 210 | 680 |
| **TOTAL** | **$1200** | **$3300** | **$7700** |

a C&EN estimates based on analyst reports and company projections. b Not yet approved but may reach market in 1991.
**Source:** Consulting Resources Corp. and C&EN estimates

## Good and bad news in biotechnology patents

For commercial development, scientific advances in biotechnology need to be coupled with intellectual property protection. In 1989, 935 U.S. biotechnology patents were issued in the pharmaceutical/health care area, according to a survey by the Pharmaceutical Manufacturers Association. Of those, 177 involved genetic engineering, with a sizable majority (83%) of U.S. origin and 47% from U.S. companies. Yet these make up only a small portion of biotechnology patents.

More than 7000 biotechnology patents were issued or abandoned by the U.S. Patent & Trademark Office in 1989, according to a September 1990 report by the U.S. General Accounting Office. However, the report notes, more than 18,500 applications were still pending. The sheer volume of biotechnology patent applications has made PTO's job difficult and has meant that biotechnology companies are facing long delays in gaining patent protection.

The average processing time of a biotechnology patent application, as calculated by PTO, is slightly more than 26 months, as compared with 19 months for other technologies. However, the time to process actual inventions from the original date of filing was more than 35 months, according to the GAO report. And, says GAO, decisions on genetic engineering-based biotechnology patents required about 44 months.

The GAO report concluded, "Unfortunately, despite PTO actions designed to accelerate decisions on biotechnology patents, processing delays continue for a growing backlog of biotechnology patent applications." The backlog of unexamined biotechnology patents grew 33% to about 8200 by the end of the first half of 1990, with 41% being more than a year old.

PTO has addressed the backlog and delays by increasing the number of biotechnology patent examiners. By the end of 1990, the number had risen to about 140 and is expected to increase to at least 200. Charles E. Van Horn, former head of PTO's biotechnology area and now special assistant to the commissioner, commented at ACS's national meeting last August in Washington, D.C., on the difficulty in attracting and retaining examiners, particularly in having enough experienced senior examiners to train new hires. Some training is being provided through a joint project put together by PTO, lawyers, industry, universities, and trade associations. Van Horn indicates that 1992 is no longer projected as the year in which the pendency of biotechnology patents will be reduced to the targeted 18 months. A more realistic estimate, he says, is now considered to be some time in 1993 or 1994.

cumulate to fight infection. The enzyme appears to be effective in thinning out infected mucus, and might also find application in pneumonia, bronchitis, and emphysema.

With three products on the market, Genentech leads the biotechnology industry in having become a fully integrated biopharmaceutical company. Its experience getting there illustrates how sensitive investor outlook is, often aggravated by mismatched expectations and reality, to the ups and downs of product development.

"The consequence is to end up with one of the most successful new drugs ever introduced, but which is commonly viewed as a great failure just because it didn't turn out to be a billion-dollar drug in its third year," says Shamel of Consulting Resources. An early delay in FDA approval, a prolonged and ultimately unsuccessful patent battle overseas, and results of the GISSI-II trial hurt the outlook for TPA and caused stock prices to rise and then fall. Ironically, Genentech's products, not including those under license to others, account for nearly a third of the industry's sales.

The 15-year-old company startled the biotechnology industry with the announcement in February 1990 that Swiss-based Roche Holdings, parent of Hoffmann-La Roche, was acquiring a 60% interest in the company. Hoffmann-La Roche has connections with at least half a dozen of the upper-tier biotechnology companies as it actively licenses products. Sweetening the deal was the promise to allow Genentech to operate independently for at least a few years. Roche has an option through 1995 to acquire all remaining shares.

Genentech wanted to free itself from quarterly earnings pressures, considered at odds with long-term commitment to R&D. The Roche merger also came at a time when major pharmaceutical firms themselves were seeing the need to consolidate. Genentech's R&D spending was already about 40% of sales and its next products still had to make it through later stages of clinical trials and FDA approval. The $2.1 billion deal with Roche included nearly $500 million in capital.

Views on the merger are diverse. But, the overall impact of "losing" an industry leader thought to be able to rival major pharmaceutical firms has been significant, leaving many biotechnology companies asking whether the goal of becoming a stand-alone, fully integrated biopharmaceutical company is either desirable or possible.

Another company started a little more than a decade ago is Biogen. Like Genentech, the 13-year-old company licensed off rights to its early developments. Biogen's 1989 profitability was derived primarily from licensees' sales of five products: $\alpha$-interferon, a hepatitis B vaccine and a diagnostic, $\gamma$-interferon, and $\beta$-interferon. In 1990, revenues increased 45% to $59.4 million, with about 76% coming from royalties and product sales.

Biogen licensed its $\alpha$-interferon to Schering-Plough, which has a cross-licensing agreement and shares the market with Hoffmann-La Roche. In 1990, Schering-Plough's revenues from $\alpha$-interferon almost doubled and are estimated at about $150 million worldwide. The product is marketed overseas with approvals in 57 countries for 16 indications.

Once expected to be a cure-all for cancer, $\alpha$-interferon has been approved in the U.S. for only three diseases—hairy cell leukemia, affecting only a few thousand individuals; AIDS-related Kaposi's sarcoma; and genital warts. However, its use is expected to continue growing in at least half a dozen named uses in the areas of cancer and hepatitis. An FDA advisory committee recently

recommended approval of Schering-Plough's product for hepatitis C.

Increasing royalties from hepatitis B products also contributed greatly to Biogen's growth in revenues. A license for the vaccine was granted to SmithKline Beecham, which launched its product in late 1989. Merck, a licensee of Chiron and cross-licensee of Biogen, introduced a genetically engineered hepatitis B vaccine in July 1986.

"There have been a couple of phases of Biogen," says Alan W. Tuck, the firm's vice president for marketing and business development. "There was the early science, which has been licensed off, and the income from those products is paying for its own R&D today." Strategic alliances with major pharmaceutical companies play significant roles in advancing product development by providing resources and expertise beyond research. Within the structure of an alliance, biotechnology companies may find the incentive and resources to gradually build and train their own clinical development, regulatory, manufacturing, and marketing and sales forces without having to bet company survival on the launch of a single product.

As leverage is built up through new product developments and a supporting infrastructure, there is often a progression from straight licensing deals, to licensing and supply agreements, into comarketing, and eventually to retaining proprietary products. "Where it makes sense, Biogen will continue to do business deals, particularly in some of the international markets, for a time anyway," says Tuck. "But what the company now does most of the time is retain some comarketing rights. The first focus now is to develop products for Biogen."

Through agreements with other companies, Biogen is marketing $\beta$- and $\gamma$-interferon, having cross-licensed rights to various $\gamma$-interferon patents with Genentech. Sales of Biogen's $\gamma$-interferon as a treatment for rheumatoid arthritis began in Germany in 1989 through a marketing agreement with the German pharmaceutical firm, Rentschler. In 1990, Shionogi, a Japanese pharmaceutical licensee of Biogen, launched the product for the treatment of renal cell cancer in Japan. Clinical trials are under way in the U.S. and Europe for these and other inflammatory diseases and cancer.

Whether $\gamma$-interferon will be retained by Biogen as a proprietary product in the U.S. will depend somewhat on what indication is approved first and the size of the market, says Tuck. After some early approvals, the market for $\gamma$-interferon likely will expand over the next five to 10 years, he believes, although its benefit in specific diseases, as well as dosage and treatment regimens, have yet to be determined.

Natural $\beta$-interferon is sold in Germany through Rentschler. A recombinant form has been licensed to Asta Pharma, a divison of the German chemicals and precious metals giant Degussa, in Europe outside of Germany, and is in Phase II trials for the treatment of viral infections. Biogen has retained certain comarketing rights and will supply it through its affiliate, Bioferon. In the U.S., Biogen is developing $\beta$-interferon itself and expects to enter clinical use soon as an agent against cancer and viral diseases.

Proprietary developments include hirulog, CD4, and a new program in endothelial cell receptors, which play a role in inflammatory conditions. Hirulog, a chemically synthesized peptide based on the structure of a natural anticoagulant found in the medicinal leech, is moving into Phase II trials. Potential uses include those for heart attack, unstable angina, and deep-vein thrombosis.

Recombinant soluble CD4 has been shown to inhibit in-vitro viral activity. It is moving ahead in trials, indicates Tuck, although, as others have found, it is somewhat slower than expected in showing effectiveness. According to Biogen, CD4 has been found to have no limiting toxicities and generally to be well tolerated in Phase I and II trials. "CD4 may have a place in the world of AIDS as a long-term treatment in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combination with other products," says Tuck, such as zidovudine (AZT) or dideoxycytidine.

Undergoing an evolutionary process similar to Biogen is Chiron. In 1986 the 10-year-old company's hepatitis B vaccine, licensed to Merck, became the first biotechnology vaccine to be approved. Whereas Merck took over development, manufacturing, and marketing of the vaccine, Chiron used the basic technology in developing its diagnostics and vaccine businesses. Royalty income from the hepatitis B vaccine, with a total worldwide market of about $200 million, as well as income from its ophthalmics subsidiary and a joint diagnostics business with Ortho Diagnostics brought the company into profitability this year.

Chiron has established itself in the hepatitis C diagnostic area with a recent product approval. Hepatitis C is a high-priority research area in vaccine development for Biocine, the company's 50-50 joint venture with Ciba-Geigy. The most likely therapeutic products to reach market from Chiron are all in the 1994 to 1995 time frame, says Larry Kurtz, a spokesman for Chiron. These are a herpes simplex II vaccine, insulin-like growth factor (IGF), and antitumor necrosis factor (anti-TNF).

Anti-TNF is targeted at septic shock in which bacteria invading the bloodstream start a cascade process in the immune system. As part of this process, tumor necrosis factor, a highly toxic natural protein that can attack tumors, is released and can result in tissue damage. Anti-TNF is a natural receptor that binds to TNF to inactivate it and to help shut down the response. Anti-TNF offers an advantage in that it can deal with septic shock caused by either gram-negative or gram-positive bacteria, says Kurtz, unlike antibodies aimed only at endotoxins released by gram-negative bacteria. Anti-TNF has been licensed to Bayer and is in Phase II and III development by the Cutter Biological group of Bayer's Miles Laboratories.

Chiron has retained manufacturing rights to IGF, but has licensed to Ciba-Geigy, which is conducting clinical trials and will market it. IGF is a very general growth factor, stimulating the growth of bone, tissue, connective tissue, and muscle. Phase II trials are under way in three areas—type II diabetes to suppress the overproduction of insulin, acute kidney failure to improve kidney flow, and catabolic states as a result of trauma. A long-term goal is to investigate its use in osteoporosis and some wasting syndromes. Genentech also is testing IGF in early trials.

A herpes vaccine is being developed by Biocine and is currently in Phase II trials for use as a therapeutic. "Most people only think of vaccines as preventive," says Kurtz. "However, there is emerging evidence that you can use a vaccine approach, that is the injection of a mimic virus, in combination with an adjuvant immunomodulator to boost the [immune] response in already infected individuals." The adjuvant in this case is an immunomodulator from Ciba-Geigy called muramyl dipeptide. This approach also is being used for a therapeutic AIDS vaccine.

Results from a study in Switzerland in 1988 and 1989 for the AIDS vaccine were not definitive, says Kurtz, but encouraging enough to proceed to further trials. The vaccine has been reformulated, the adjuvant enhanced, and Phase I trials were begun in the U.S. last month. The viral part of the vaccine is a nonglycosylated version of the HIV gp120 surface protein. Genentech is conducting similar studies with a native gp120 protein, says Kurtz, and MicroGeneSys is using the gp120 precursor protein called gp160. "At this point in the AIDS area, there is nothing but therapeutic [vaccine] trials under way as nobody has yet mounted a true preventive clinical trial."

Even before Genentech's merger with Roche, the 11-year-old Amgen was emerging as a top-tier biotechnology company. With EPO, Amgen became the second biotechnology company to make the transition to a fully integrated, independent biopharmaceutical company. EPO, a naturally occurring protein that stimulates the production and differentiation of red blood cells, was approved by FDA in mid-1989 for the treatment of chronic renal failure patients on dialysis. U.S. sales currently surpass that of any other single biotechnology product.

EPO rapidly penetrated the market and now is used by more than 82,000 dialysis patients in the U.S., says Harry F. Hixson Jr., until very recently the president of Amgen. "Amgen has penetrated the U.S. market something in excess of 90%," he says, adding that current U.S. sales are more than $300 million a year. EPO is also being sold by licensees—in Europe by Johnson & Johnson subsidiary Cilag Pharmaceuticals, and in Japan by Kirin Brewery—for about another $300 million in sales.

Amgen has been embroiled in prolonged U.S. patent litigation with Genetics Institute in one of the first cases to test the scope and valid-

Genetics Institute photo

*Researcher in mammalian cell culture lab helps to develop methods for scaling up production of drug products*

## Biotech products fit in several broad classes

**Colony-stimulating factors (CSFs).** Immune system growth factors that control the differentiation, growth, and activity of white blood cells. GM-CSF stimulates the production of both granulocytes and macrophages, helping to overcome immune deficiencies and fight infection. Other proteins having narrower responses include G-CSF and M-CSF.

**Erythropoietin (EPO).** A protein produced in the kidney that stimulates red blood cell production. It is used to treat anemia linked with renal failure and also may find use in anemia resulting from chemotherapy or therapy for AIDS.

**Blood factors.** Proteins involved in the multistep process of blood clotting. Some, such as Factor VIII which is deficient in persons with hemophilia A, have been isolated from blood plasma for many years, recombinant forms could offer treatments as effective and contamination-free.

**Growth factors.** Proteins responsible for directing the differentiation and production of various cell types. Epidermal growth factor (EGF) is expected to find use in wound healing. Platelet-derived growth factor (PDGF) is involved in collagen deposition in tissue repair. Insulinlike growth factor (IGF) has fairly broad activity in promoting tissue growth and is being investigated for nutritional and growth disorders.

**Human growth hormone (HGH).** A hormone secreted by the pituitary gland used to treat growth deficiencies in children. Recombinant HGH is purer, less costly, and more available than isolated natural versions.

**Interferons.** Broad-acting agents, produced by a variety of cells, that interfere with viral infection and may control the spread of some cancers. $\alpha$-Interferon's use is expanding in the treatment of various cancers and is being investigated for use in AIDS therapy. Also under study are $\gamma$- and $\beta$-interferon for use in AIDS, cancer, and some infectious diseases.

**Interleukins (ILs).** Immune system hormones, or cytokines, that stimulate and regulate the growth and function of a wide variety of white blood cell types. At least 10 interleukins have been discovered. IL-1, IL-2, and IL-3 lead in development in diverse areas such as cancer, wound healing, immune deficiencies, and AIDS.

**Monoclonal Antibodies (mAbs).** Antibodies that are specific to certain antigens or cell types; can be used in several ways. Naked mAbs can directly attack foreign toxins, viruses, or cancer cells. mAbs also can be used to deliver radioisotopes (as therapeutics or imaging agents) or other drugs to specific targets.

ity of patents related to recombinant and natural proteins. Amgen holds patents to genetic sequences, vectors, and host cells for producing recombinant EPO. Genetics Institute holds a patent to the purified protein. In late 1989, claims of both patents were found to be valid and infringed by the other party. With an apparent stalemate, a cross-license between the two firms was ordered by the court. In early 1990, both companies appealed and hearings were held later in the year. These are expected to result in a ruling from the appeals court at any time.

Directly related to the dispute between Amgen and Genetics Institute are issues of orphan drug status and patent protection, which became focuses of the biotechnology industry this past year. In 1990, two bills were proposed by Rep. Rick Boucher (D.-Va.) aimed at increasing protection against foreign infringement. These bills sought to override a precedent that was set in a case involving a production process for carbamate pesticides. In that case, it was found that a process may be considered obvious and unpatentable even if it employs or produces a novel and unobvious (patentable) material. Thus, as biotechnology or any technology matures, obtaining process patents becomes more difficult.

"There is a great need for increased intellectual property protection for the biotechnology industry," says Hixson. "There are certain aspects of process patent case history that were developed for older technologies that are being applied inappropriately to biotechnology."

Under U.S. law, a product made abroad and imported into the U.S. cannot be stopped unless it violates a valid process patent, even if it is made with a patented material. Genetics Institute's licensee, Chugai Pharmaceuticals, was not found to infringe Amgen's patents and is able to make EPO abroad, import it, and sell it in the U.S. Patents covering genetic sequences and host cells used in producing recombinant proteins have not been interpreted as process patents, explains Hixson.

IBA has supported changing patent law, believing it's needed to help the U.S. maintain its competitive stance in biotechnology, and will "try very hard in the 102nd Congress to bring that about," says Godown of IBA. "Patents are the very lifeblood of biotechnology," he adds. "Not only do they spell protection, but they spell the ability to raise capital, make business plans, build manufacturing facilities, market, and build a company."

The former chief executive officer of Cetus, Robert A. Fildes, called the proposed changes unnecessary, protectionist, and destabilizing by virtue of the uncertainties that would be introduced into the industry. IBA's position on the Boucher bills, and its initial opposition to amendments in the Orphan Drug Act, caused Cetus and Genetics Institute to resign from the trade association.

The Amgen/Genetics Institute dispute is complicated further by Amgen's having orphan drug status and effectively blocking Genetics Institute with an application pending for the same indication. "There are a few drugs, and [EPO] is one, where the criteria still permit a reasonably high revenue base," says Hixson. "But the law itself is very sound and offers appropriate incentives to a number of manufacturers and a number of important drugs have been developed with that strictly in mind. The law is there, it's in place, and you must be prudent and take advantage of those laws so that someone doesn't use them to take advantage of you."

Genetics Institute's EPO is being sold for dialysis patients in both Japan and Europe by licensees Chugai Pharmaceuticals and Boehringer

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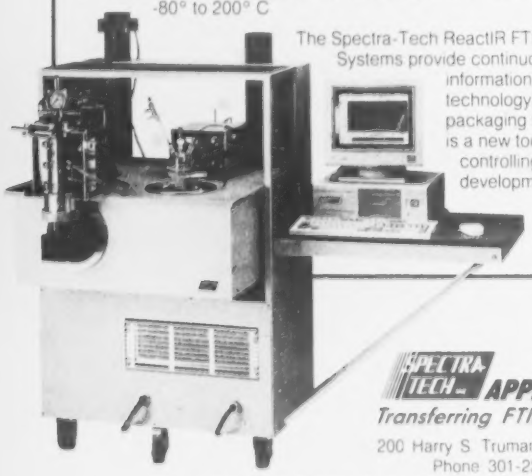

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Mannheim, respectively. The company began petitioning FDA about two years ago with requests for approval under the Orphan Drug Act.

In a decision early this year, FDA denied two claims that related to the patient population for EPO. However, two other claims remain open. One centers on Genetics Institute's product being kept off the market, when the company holds a valid and infringed U.S. patent, by another product because of orphan status. Congress' intent in establishing orphan drug law, says Genetics Institute, was that patent law should have precedence in the event of such a conflict. In response, FDA has indicated that in the absence of a definitive decision on patent rights pending outcome of the appeals, no decision could be made.

The other outstanding claim relates to the question of whether the two products can be defined as different under orphan drug law. "It's clearly been reported that the actual carbohydrate structures of the two forms of EPO are different," says L. Patrick Gage, executive vice president of Genetics Institute. Very simple changes or deletions in the carbohydrate structure, which can depend on whether a protein is produced in bacterial, yeast, or mammalian cells, can completely inactivate the molecule, he explains. "But there is debate about how important other changes might be, like those clearly present between the two molecules."

Most of the market expansion for EPO will come about through new uses. Amgen's U.S. licensee, Ortho Biotech, just received its first U.S. approval for EPO in the treatment of AIDS-related anemia and expects to launch the product this month. Ortho and affiliated Johnson & Johnson companies hold the rights to most indications in the U.S. and to all worldwide, marketing EPO in 43 countries. A very large market for which Ortho hopes to file applications both inside and outside the U.S. in 1991 is anemia associated with cancer and chemotherapy. Other areas being looked at include anemia in predialysis patients and rheumatoid arthritis, and autologous blood donation.

Despite its record sales, EPO actually offers a limited opportunity for

*Immunex technician checks product*

Amgen because it retained only U.S. manufacturing rights and the U.S. dialysis market. The firm's next major product will be one of the colony-stimulating factors (CSFs), a new class of drugs that play a role in white blood cell production. CSFs are finding application in a wide variety of diseases, targeted primarily at increasing the ability of the immune system to fight infection.

Amgen filed an application with FDA in late 1989 for a CSF that promotes the production of granulocytes (G-CSF) as an adjunct to chemotherapy in correcting deficiencies of white blood cells called neutrophils (neutropenia). With a very rapid turnaround, G-CSF was recommended for approval by an FDA advisory committee in December 1990.

U.S. sales of CSFs are expected to be $200 million by the mid-1990s and $650 million or more by 2001. Amgen's initial U.S. cancer market for G-CSF is expected to be large. However, the importance of G-CSF is more than just its potential sales, Hixson says. The company has kept full marketing rights in the U.S., Canada, and Australia, and comarketing rights in Europe with Hoffmann-La Roche for a five-year period, after which Amgen has the right to assume all marketing itself.

Early in 1990, Amgen and Hoffmann-La Roche filed jointly in Europe for approval of G-CSF. The European regulatory group, the Committee for Proprietary Medicinal Products (CPMP), issued a favorable opinion on G-CSF this month. Amgen hopes that it will be followed by a series of approvals in the individual European countries throughout the year. Licensee Kirin also filed in late 1989 for approval in Japan. As with other broad-acting biological response modifiers, G-CSF is expected to expand into other uses. Amgen has active clinical programs in the areas of bone marrow transplants, chronic neutropenias, and preclinical work looking at G-CSF's antiinfective or antibacterial properties.

Amgen's R&D spending approaches 30% of sales, according to Hixson. The money is being used in part to develop tissue growth factors, two neurotrophic factors, and another early-acting blood cell growth factor called stem cell factor (SCF). Preclinical studies on SCF have shown that it may find use in treating bone marrow damage, and Amgen is trying to get it into clinical trials as soon as possible.

The tissue growth factors include epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) for use in wound-healing applications. Chiron also has EGF and PDGF in Phase II trials. Both companies indicate that clinical trials have been somewhat more difficult than expected and that it will take time to develop drug delivery systems.

Direct competition for Amgen's G-CSF is expected from Chugai Pharmaceuticals, which, says Hixson, has a filing for G-CSF in Japan. Chugai is conducting clinical trials in Europe, but has not initiated any activity in the U.S., he adds. Initial competition in the U.S. and Europe is primarily expected from another CSF that stimulates the production of granulocyte and macrophage (GM-CSF) white blood cells.

Genetics Institute granted a worldwide license for GM-CSF to Sandoz, which in turn established a codevelopment and comarketing agreement with Schering-Plough. An interference has been declared by the U.S. Patent Office between patent applications filed by Genetics Institute and Immunex. Genetics Institute indicates that it was on the basis of its patent position that Schering-Plough took a cross-license. Immunex also considers itself to have a strong position.

Genetics Institute's GM-CSF is awaiting approval in the U.S. as an adjuvant to chemotherapy and, according to the company, its licensees had a closed session review with the Biological Response Modifiers Advisory Committee in December. As a broad-acting immune system stimulator, GM-CSF is under development by both Genetics Institute and its licensees and Immunex for several diseases.

Although considered a major biotechnology company, Genetics Institute has not yet marketed a proprietary product in the U.S. Its licensee, Baxter Healthcare, has filed an application with FDA for approval of Factor VIII, the blood-clotting factor deficient in individuals with type A hemophilia. A few years ago, Genetics Institute and Genentech, with its licensee Cutter Biological, cross-licensed both patents and orphan status for Factor VIII. The recombinant forms are expected to enter an already large market, offering an alternative to plasma-derived Factor VIII.

Genetics Institute's first proprietary product, having retained all U.S. and European rights, is macrophage colony-stimulating factor (M-CSF). This product is cross-licensed in a royalty-free agreement with Cetus. For different uses, says Gage, it is in Phase I or Phase II clinical trials. Three areas under investigation in which M-CSF might be useful in stimulating immune system defenses are infectious diseases, hypercholesterolemia, and cancer.

In 1990, Genetics Institute spent about $61 million on R&D. The company has started an active program in bone morphogenetic proteins (BMPs), which stimulate the formation of bone and cartilage. Preclinical work to be reported on this year is going to be "quite dramatic," Gage says, and will draw attention to what he sees as a new wave of potential products, expected to be useful in a wide variety of orthopedic, surgical, and dental conditions. One bone growth protein, BMP-2, is expected to enter clinical trials in late 1991 or early 1992. The compa-

ny has kept worldwide manufacturing rights and North American marketing rights while setting up a U.S.-based development partnership and a 50-50 joint venture in Japan with Yamanouchi Pharmaceuticals.

According to Genetics Institute, it has stopped work on TPA and is evaluating further development of its second-generation product, novel plasminogen activator (NPA) in the U.S. and Europe. In a patent dispute with Genentech, a jury found in April that Genetics Institute and Wellcome infringed Genentech's TPA patents. However, the companies are awaiting a judgment not withstanding the verdict in that case. "One should expect an appeal of that judgment if it goes against us," says Gage.

Broad interpretation of the patent claims of Genentech's included second-generation molecules such as NPA, which differs from TPA by a number of deletions in the amino acid sequence. Such modifications in amino acids and glycosylation are designed to alter the activity, side effects, and immunogenicity of proteins. Genetics Institute had licensed NPA to Wellcome in 1989. In May, following both the jury verdict and the results of the GISSI-II trial, Wellcome decided to drop development.

Immunex may be in the best position to provide competition for CSF products. Having recently received a positive recommendation for approval from the Biological Response Modifiers Advisory Committee, Immunex could reach the market first with GM-CSF, but only for a limited disease indication. It has obtained orphan drug status for use in bone marrow transplant patients, but most companies, including Immunex, suggest that this will not be a significant factor in blocking the market—GM-CSF is expected to find use in several diseases. The timing of entry to the market may be advantageous in gaining product acceptance and market share. And, once approved, physicians are free to prescribe a drug for conditions outside the approved indication.

Immunex filed a product license application in February 1990 under a program for expedited review and only six months later had its first appearance before the FDA committee. Although initially it did not receive a positive recommendation, the company was allowed to make GM-CSF available to seriously ill patients under a treatment investigational new drug application. By December 1990, at a second meeting, Immunex was able to provide enough supporting data for the committee to recommend approval.

"Immunex has been fairly pleased with the way [FDA] has responded to our application. It was submitted less than a year ago and here [Immunex is] on the verge of an approval," says John A. Spears, vice president and director of sales and marketing at Immunex. "That's pretty fast in the scheme of things." Based on experience in the drug industry, the time from recommendation to approval can be anywhere from three to six months, he adds, but it is impossible to speculate if and when approval will be granted. Immunex and its partner Hoechst Roussel will comarket GM-CSF under different brand names in the U.S.

Ten-year-old Immunex has remained focused on immunological therapeutics and the launch of a first, proprietary product (C&EN, Dec. 17, 1990, page 8). Its broad area of development includes interleukins (ILs), immune system hormones directing cell growth, many of which it has in clinical trials. The company also has a very active, although still preclinical, program in interleukin receptors, which may find use in controlling certain inflammatory conditions.

Immunex has IL-1$\beta$ in Phase II trials for wound healing, IL-1$\alpha$ in Phase I as a bone marrow protectant in radiation or chemotherapy, and IL-4 in trials for cancer therapy. IL-2 has been licensed to Hoffmann-La Roche, which has its product in clinical trials for renal cell cancer and melanoma. Currently in Phase I trials is IL-3 for neutropenia and platelet deficiencies.

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Combinations of interleukins and CSFs have been attracting attention. Immunex has developed a fusion molecule of IL-3 and GM-CSF that has shown promising in-vitro results, says Spears. However, Genetics Institute holds patents to IL-3, licensed to Sandoz and in Phase I and II trials in the U.S. and Europe, said to cover first- and second-generation molecules including "IL-3 proteins produced using all or part of the IL-3 DNA sequence and showing IL-3-like properties."

Whereas Immunex responded favorably to the FDA advisory committee's questions, the final outcome on Cetus' late-1988 application for IL-2, the first much hyped, but yet unproven, interleukin to come before the agency, is unknown. Cetus' experience, as well as first-time experiences of other biotechnology companies, is being closely scrutinized for insight into the regulatory process. At the same meeting with Immunex in July 1990, the Biological Response Modifiers Advisory Committee did not recommend for or against approval for IL-2 in the treatment of renal cancer.

"The committee asked the company to work with FDA and identify subsets of patients who were more likely to show a clinical response to the drug, and less likely to suffer severe adverse events," explains Ed Kenney, director, biological therapeutics, for Cetus. IL-2 has rather toxic side effects and a mortality rate of a few percent, not unlike other chemotherapeutic treatments. In addition, a response to IL-2 is seen in about 20% of patients, with only a few percent showing complete remission. These conflicting facts complicate the issue because IL-2 is the only drug to have ever shown any lasting activity in otherwise fatal renal cell cancer, he adds.

The company faced at least two problems regarding its clinical trial data. Because a life-threatening disease with no existing treatment was targeted, explains Kenney, it can be difficult to design a placebo-controlled, double-blind study that is preferred by FDA. Instead historical comparisons, which have been used before, to $\beta$-interferon trials on kidney cancer patients were submitted. Supporting data for IL-2 used in combination with lymphokine-activated killer (LAK) cells was not accepted by the committee. LAK cells are disease-fighting white blood cells isolated from a patient, grown in the presence of IL-2, and then reinfused. FDA has not defined how it will approach activated cellular therapies that have been described as both drugs and delivery systems.

The advisory committee's response was damaging. Market estimates for IL-2, whether realistic or not, once ran as high as several hundred million dollars, but now are more conservative. Shortly after the committee met, the company's stock dropped from just over $22 to about $8.00 per share. Shareholders also filed suit regarding disclosure about IL-2's efficacy, and its potential for FDA approval and sales. In the wake of events, Cetus chief executive Fildes resigned, and the company reduced staff and cut costs.

Cetus clearly leads in the development of IL-2 as the only company with an application pending in the U.S. and having received approval in nine European countries for renal cell cancer. Industry executives explain that it is not uncommon for products to be approved faster in Europe, which has been called a less harsh regulatory environment, than in the U.S.

Long ago cross-licensed in agreements between various companies, IL-2 is in Phase III trials for various cancers and in early trials for AIDS by Cetus and others. IL-2 plays a central role in activating T cells, which are a fundamental part of the immune response, Kenney says, and has shown activity in several broad areas including cancer and some infectious diseases.

The possible first approval of IL-2 in the U.S. has been delayed at least several months. Cetus has been working with FDA, but has not been scheduled to meet again with the advisory committee or FDA to dis-

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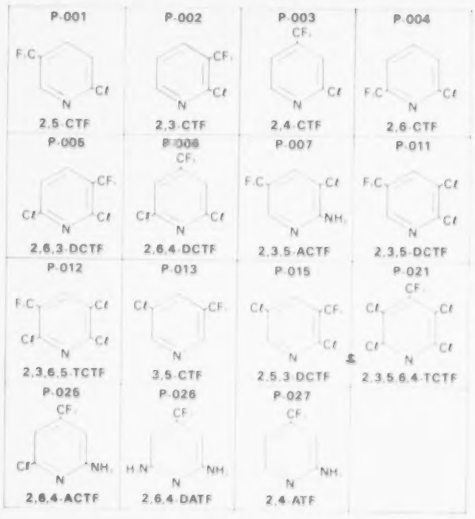


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cuss approval. "Cetus believes it has identified [those] groups of patients," says Kenney. "It will be up to us to convince FDA and/or the advisory committee."

The 20-year-old Cetus long appeared to be betting its financial success on IL-2 as its first proprietary U.S. drug product, and winning approval is still a priority. The company has spent nearly a decade and more than $100 million on developing IL-2. In the fiscal year ending June 1990, the company reported a net loss of nearly $62 million on revenues of about $39 million. The company had been investing heavily in regulatory development, and in setting up its manufacturing and marketing efforts for IL-2.

Sales of IL-2 in Europe have been growing, Kenney says, and the company is seeking to expand IL-2 into other uses. A European filing for melanoma is being prepared. Cetus also has entered into a European copromotion agreement with Hoffmann-La Roche for IL-2 and $\alpha$-interferon, which find use in combination, including subcutaneous use.

"The future of IL-2 is in being used in [new indications]," says Kenney, "and it will come to be used in combinations either with other naturally occurring products or very likely with chemotherapy." Cetus also has a "second-generation" IL-2 that has polyethylene glycol molecules attached, in clinical trials for cancer and possibly in AIDS. "The animal data suggested that it did improve the therapeutic index; in other words, there was an increased efficacy and a reduced toxicity," he says. "And that's what we hope to see in humans."

After IL-2, Cetus has no major products nearing the market in the short term. The company has dropped development of a second immunotoxin that was in clinical trials—work on an earlier one was halted a few years ago—because of problems with toxicity. Tumor necrosis factor, a toxic and somewhat difficult to work with immune system agent effective against tumors, has also been dropped.

Longer term products with promise for Cetus are M-CSF, which has shown antiviral, antibacterial, and antifungal activity preclinically, and also appears to have use in cancer and possibly in wound healing. The company is making the difficult strategic decision of which indications to pursue, Kenney adds. M-CSF is about to enter Phase II trials for fungal infections.

The company also has a monoclonal antibody (mAb) for use in sepsis and septic shock patients. Cetus will face very strong competition from Xoma and Centocor, two companies focused on monoclonal antibodies that have both filed product license applications for products for sepsis. "It [will be] a competitive area," says Kenney, "but I draw the analogy with the antibiotics market—a very competitive area, but also a huge commercial area. And, if they follow anything like antibiotics, there will be some niching or positioning of them differently based on where they work."

Centocor is preparing for the launch of its mAb product, which binds to and inactivates endotoxins produced by gram-negative bacteria, the cause of about two thirds of sepsis cases. An application was filed with FDA in September 1989, shortly thereafter followed by a filing with the CPMP in Europe. "Sepsis and septic shock are very similar severe illnesses where people deteriorate very rapidly," says Elizabeth E. Tallett, executive vice president of Centocor and president of its pharmaceutical division. "Most patients are treated presumptively (before the causitive agent is known), so that market would largely be open to us as a total market."

With as many as 400,000 patients, the U.S. market has been estimated at several hundred million dollars. The only existing therapy is treating the bacterial infections with antibiotics that are not always effective in preventing what can be an extremely rapid progression to shock. Depending on the severity, low-level septicemia and sepsis patients have a mortality rate of about 25%, increasing to about 75% for those who have progressed to septic shock. In combination with antibiotics, mAbs can "sponge up" endotoxins while antibiotics work to kill the bacteria, improving the mortality rate in the most ill group by 50%.

Tallett says the company is confi-

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dent of being the first to market in Europe, and very hopeful of being the first to market in the U.S. Centocor's prime competitor, Xoma, has also developed a mAb product for sepsis and has filed applications with its partner, Pfizer, in both the U.S. and Europe. Xoma will be backed by the marketing power of a major pharmaceutical firm, whereas Centocor plans do its own marketing in both the large U.S. and European markets.

Xoma holds a U.S. patent covering the therapeutic use of mammalian source antiendotoxin mAbs in the treatment of humans having gram-negative sepsis and/or septic shock. The company's patent infringement suit against Centocor will go to trial in July, says Patrick J. Scannon, president of Xoma. Tallett says Centocor is extremely confident of having a very strong patent position.

Xoma's product is a murine mAb. According to Tallett, Centocor's is the first human mAb developed for the market and produced on a large scale. The mAbs also may be "humanized," where human segments replace some (a chimeric antibody) or most (fully humanized) of the immunoglobulin structure of a murine mAb.

Tallett says the Centocor product offers advantages in being nonimmunogenic, since murine mAbs may cause an immune response in humans. "It also has considerable benefit in terms of the effectiveness—the bottom line is 'human works better in humans,' " she says.

Scannon of Xoma believes immune reactions will not be a significant factor in treating sepsis. "If [patients] do develop an immune response [to the murine mAb], it occurs after the treatment is over and is not associated with any side effects," he explains. Most surviving patients make their own endotoxin antibodies and will only ever have one episode of gram-negative sepsis in their lives. "So it will have no effect on the first course therapy and, if you are in the vast majority of patients—something like 95% or more—who will not have a repeat course of therapy, it is not an issue."

These would be the first therapeutic products for either company. Along with marketing partner Ortho Biotech, Xoma has filed an application with FDA and is preparing one in Europe for a mAb, CD5, for use in graft versus host disease. CD5 is a murine mAb chemically linked to an enzyme, Ricin A chain, which can bind to and eliminate T lymphocytes. As with other targeted therapies Xoma is developing, the mAb is a delivery system that allows the enzyme not only to be effective but also site specific.

In graft versus host disease, the goal is to remove mature lymphocytes found in donor marrow that will attack the host body, explains Scannon. Immature immune cells in the transplanted marrow can become tolerant of the host environment. It is currently an orphan drug indication with about 3000 to 4000 transplants per year, but Scannon expects the market to grow rapidly. "The most fundamental reason is that if you can control graft versus host disease, [then] bone marrow transplantation works. ... It's becoming a true therapy for the treatment of leukemias and a number of other blood-borne diseases."

Xoma has retained manufacturing and marketing rights to CD5 for a number of other diseases mediated by T lymphocytes. For example, Phase III trials are about to start in rheumatoid arthritis. Ortho, which already sells the only mAb product approved—one to prevent kidney transplant rejection—is involved in developing CD5 for organ transplant rejection and another yet unnamed indication. "That is an area [where] Ortho has a great deal of expertise," says Scannon, "and one that Xoma was not going into. So Xoma's relationship with Ortho has actually expanded its opportunities."

Although also developing and selling mAb-based imaging agents, Centocor's next nearest-term therapeutic is a chimeric mAb fragment that acts as a platelet aggregation inhibitor. It is in early clinical trials for use with thrombolytic agents in heart attacks, to prevent reocclusion and restenosis after balloon angioplasty, and in treating unstable angina. Centocor also is investigating anti-TNF and anti-CD4 antibodies, for possible use in autoimmune conditions such as rheumatoid arthritis and multiple sclerosis, and another directed at gastrointestinal cancers either alone or in combination with radioactive isotopes.

Cytogen, which has applications filed for approval of two mAb cancer imaging agents that deliver radioisotopes to specific tumor sites, is a leader in this area. The company is testing similar design radioisotope-based therapeutic agents in Phase I—soon moving into Phase II—trials, which have yet to be studied for efficacy in ovarian and gastrointestinal cancers.

Cytogen's products employ a proprietary "linker" technology, generally some sort of chelating group attached to the mAb, which binds a radioisotope and delivers it to specific tumor sites. The company has licensed its linker technology to major pharmaceutical companies interested in tying chemotherapeutic agents to mAbs for site-specific delivery.

A mAb development goal is achieving low dose levels when the linker does not interfere with the ability of the antibody to find its target and bind effectively. Because of the specificity and potentially lower doses required, mAb agents may offer an advantage in reducing the side effects common with chemotherapy. For the same reason, mAb agents are expected to be unlike chemotherapy, which targets any rapidly dividing cells in the body and thus can damage healthy cells.

Like other biopharmaceuticals, the regulatory route for mAb products is mostly uncharted and has yet to fall into a pattern. The time it will take for approvals and the eventual success of these and other products is still unknown. As more products are approved, second-generation versions developed, and biopharmaceuticals are established in positions in pharmaceutical markets, companies can expect to face new issues along with continuing debates on patents and orphan drugs. Most industry and outside observers are anticipating that the costs of relatively expensive, yet novel, biotechnology drug products will have impact on markets, competition, and profits, particularly as health care costs and reimbursement issues become even more critical. □